UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Washington, DC 20460

AUTHENTICATION

I, Lynn Vendinello, attest that I am the Director of the Communications Services and Information Division, Office of Program Support of the United States Environmental Protection Agency (EPA) and that the attached documents are true, correct, and compared copies of the file copies in my legal custody, consisting of:

1. **August 7, 2019, Letter Regarding EPA No Longer Approving Labeling, Including Prop 65 Warning (2 pages).**
2. **March 16, 2017, FIFRA SAP Meeting Minutes and Final Report – EPA's Evaluation of the Carcinogenic Potential of Glyphosate (24 pages).**
3. **April 3, 1985, Glyphosate EPA Registration Number 524-308 Mouse Oncogenicity Study (4 pages).**
4. **December 12, 1985, EPA Registration Number 524-308 Roundup / Glyphosate Pathology Report on Additional Kidney Sections (3 pages).**
5. **January 5, 1988, Monsanto Comments to Glyphosate Guidance Document (6 pages).**
6. **September 21, 2022, Withdrawal of the Glyphosate Interim Registration Review Decision (9 pages).**
7. **2013, Recognition & Management of Pesticide Poisonings (10 pages).**

Subscribed under the penalty of perjury on this 30 day of January, 2023.

Lynn Vendinello

Lynn Vendinello, Director
Communications Services and Information Division
Office of Program Support

CERTIFICATION OF TRUE COPY

I, Charlotte Youngblood, certify that I am the Acting Associate General Counsel, General Law Office, Office of General Counsel, of the United States Environmental Protection Agency; that I am the designee of the General Counsel for the purpose of executing certifications under 40 C.F.R. sec. 2.406; that I have duties in Washington, District of Columbia; and that the official whose signature appears above has legal custody pursuant to 40 C.F.R. sec. 2.406 of the original documents, copies of which are attached, as witnessed by my signature and the official seal of the United States Environmental Protection Agency.

CHARLOTTE YOUNGBLOOD

Digitally signed by CHARLOTTE YOUNGBLOOD
Date: 2023.02.02 12:44:05 -05'00'

Charlotte Youngblood
Acting Associate General Counsel
General Law Office
Office of General Counsel

Date:_____

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

August 7, 2019

Dear Registrant,

We are writing to you concerning label and labeling requirements for products that contain glyphosate.

On July 7, 2017, California listed glyphosate as a substance under Proposition 65[1], based on the International Agency for Research on Cancer's (IARC's) classification of the pesticide as "probably carcinogenic to humans." EPA disagrees with IARC's assessment of glyphosate. EPA scientists have performed an independent evaluation of available data since the IARC classification to reexamine the carcinogenic potential of glyphosate and concluded that glyphosate is "not likely to be carcinogenic to humans." EPA considered a more extensive dataset than IARC, including studies submitted to support registration of glyphosate and studies identified by EPA in the open literature as part of a systematic review. For more detailed information on this evaluation, please see the 2017 Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential[2]. Further, EPA's cancer classification is consistent with other international expert panels and regulatory authorities, including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, European Food Safety Authority, European Chemicals Agency, German Federal Institute for Occupational Safety and Health, New Zealand Environmental Protection Authority, and the Food Safety Commission of Japan.

On February 26, 2018, the United States District Court for the Eastern District of California issued a preliminary injunction enjoining California from enforcing the state warning requirements involving the pesticide glyphosate's carcinogenicity, in part on the basis that the required warning statement is false or misleading[3].

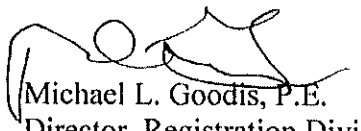
Given EPA's determination that glyphosate is "not likely to be carcinogenic to humans," EPA considers the Proposition 65 warning language based on the chemical glyphosate to constitute a false and misleading statement. As such, pesticide products bearing the Proposition 65 warning statement due to the presence of glyphosate are misbranded pursuant to section 2(q)(1)(A) of FIFRA and as such do not meet the requirements of FIFRA. In registering pesticides, EPA must determine that the labeling complies with the requirements of FIFRA including that the product

[1] California's Safe Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65) requires businesses to inform Californians about significant exposures to chemicals that, under the terms of Proposition 65, are believed to cause cancer, birth defects or other reproductive harm. *See* California Office of Environmental Health Hazard Assessment, "Proposition 65," at https://oehha.ca.gov/proposition-65.
[2] https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073
[3] National Association of Wheat Growers, et al. v. Zeise, 309 F.Supp.3d 842 (E.D.Cal.)

not be misbranded. See FIFRA 3(c)(5)(B). Therefore, EPA will no longer approve labeling that includes the Proposition 65 warning statement for glyphosate-containing products. The warning statement must also be removed from all product labels where the only basis for the warning is glyphosate, and from any materials considered labeling under FIFRA for those products.

For any pesticide product that currently contains Proposition 65 warning language exclusively on the basis that it contains glyphosate, EPA requests the submission of draft amended labeling that removes such language within ninety (90) days of the date of this letter.

Sincerely,



Michael L. Goodis, P.E.
Director, Registration Division
Office of Pesticide Programs

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

MAR 16 2017

MEMORANDUM

SUBJECT: Transmission of Meeting Minutes and Final Report of the December 13-16, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with EPA's Evaluation of the Carcinogenic Potential of Glyphosate

TO: Rick P. Keigwin, Jr.
Acting Director
Office Pesticides Programs

FROM: Steven M. Knott, M.S.
Acting Executive Secretary
FIFRA SAP Staff
Office of Science Coordination and Policy

THRU: Stanley Barone, Ph.D.
Acting Director
Office of Science Coordination and Policy

Please find attached the meeting minutes and final report of the December 13-16, 2016 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) open public meeting held in Arlington, Virginia. This report addresses a set of scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate.

Attachment

cc:

Wendy Cleland-Hamnett
Louise Wise
Stan Barone
Arnold Layne
Delores Barber
Marietta Echeverria
Michael Goodis
Yu-Ting Guilaran
Steve Knizner
Robert McNally
Wynne Miller
Jaqueline Mosby
Dana Vogel
Gregory Akerman
Jeff Dawson
Anwar Dunbar
Anna Lowit
Cathy Milbourn
Monique Perron
Linda Strauss
OPP Docket

FIFRA Scientific Advisory Panel Members

Marion F. Ehrich, PhD, DABT, ATS
David A. Jett, PhD
James McManaman, PhD
Joseph Shaw, PhD
Sonya K. Sobrian, PhD

FQPA Science Review Board Members

Kenny Crump, PhD
Laura C. Green, PhD, DABT
Eric S. Johnson, MB; BS (MD), PhD, MPH, DTPH
Barbara L. Parsons, PhD
Kenneth Portier, PhD
Aramandla Ramesh, PhD
Elizabeth A. (Lianne) Sheppard, PhD
Emanuela Taioli, MD, PhD
Daniel Zelterman, PhD
Luoping Zhang, PhD

FIFRA Scientific Advisory Panel
Meeting Minutes and Final Report
No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center,
One Potomac Yard
Arlington, Virginia

TABLE OF CONTENTS

NOTICE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act (FQPA) Science Review Board members serve the FIFRA SAP on an *ad hoc* basis to assist in reviews conducted by the Panel. These meeting minutes and final report have been written as part of the activities of the FIFRA SAP and represent the views and recommendations of the FIFRA SAP and do not necessarily represent the views and policies of the EPA, or of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the EPA or any party. In preparing the meeting minutes and final report, the FIFRA SAP carefully considered all information provided and presented by the EPA, as well as information presented in public comments.

These meeting minutes and final report of the December 13-16, 2016 FIFRA SAP meeting held to consider and review scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate were certified by James McManaman, Ph.D., FIFRA SAP Chair and Steven Knott, M.S., Designated Federal Official. The minutes and final report are publicly available on the SAP website (https://www.epa.gov/sap) under the heading of "Scientific Advisory Panel Meetings" and in the public e-docket, Docket Identification Number: EPA-HQ-OPP-2016-0385, accessible through the docket portal: https://www.regulations.gov. Further information about FIFRA SAP reports and activities can be obtained from its website at https://www.epa.gov/sap. Interested persons are invited to contact Steven Knott, Designated Federal Official, via email at knott.steven@epa.gov.

SAP Minutes and Final Report No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center
One Potomac Yard
Arlington, Virginia

James McManaman, Ph.D.
FIFRA SAP Chair
FIFRA Scientific Advisory Panel

Date: MAR 16 2017

Steven Knott, M.S.
Designated Federal Official
Office of Science Coordination and Policy, EPA

Steven M. Knott

Date: MAR 16 2017

PANEL ROSTER

FIFRA SAP Chair

James McManaman, PhD
Professor and Chief
Section of Basic Reproductive Sciences
Department of Obstetrics & Gynecology, Physiology & Biophysics
University of Colorado, Denver
Aurora, CO

Designated Federal Official

Steven Knott, MS
US Environmental Protection Agency
Office of Science Coordination & Policy
FIFRA Scientific Advisory Panel
EPA East Building, MC 7201M
1200 Pennsylvania Avenue, NW
Washington, DC 20460
Phone (202) 564-0103
Fax (202) 564-8382
Knott.steven@epa.gov

FIFRA Scientific Advisory Panel Members

Marion F. Ehrich, PhD, DABT, ATS
Professor, Pharmacology and Toxicology
Department of Biomedical Sciences & Pathobiology
Virginia-Maryland College of Veterinary Medicine
Blacksburg, VA

David A. Jett, PhD
Director, National Institutes of Health CounterACT Program
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD

Joseph Shaw, PhD
Associate Professor
School of Public and Environmental Affairs
Indiana University
Bloomington, IN

Sonya K. Sobrian, PhD
Associate Professor
Department of Pharmacology
Howard University College of Medicine
Washington, DC

FQPA Science Review Board Members

Kenny Crump, PhD
Private Consultant
Ruston, LA

Laura C. Green, PhD, DABT
President and Senior Toxicologist
Green Toxicology LLC
Brookline, MA

Eric S. Johnson, MB; BS (MD), PhD, MPH, DTPH
Professor, Department of Epidemiology
University of Arkansas for Medical Sciences
Little Rock, AR

Barbara L. Parsons, PhD
Research Microbiologist
Division of Genetic and Molecular Toxicology
National Center for Toxicological Research
US Food and Drug Administration
Jefferson, AR

Kenneth Portier, PhD
Vice President
Statistics and Evaluation Center
American Cancer Society
Atlanta, GA

Aramandla Ramesh, PhD
Associate Professor
Department of Biochemistry & Cancer Biology
Meharry Medical College
Nashville, TN

Elizabeth A. (Lianne) Sheppard, PhD
Professor and Assistant Chair of
Environmental and Occupational Health Sciences
University of Washington
Seattle, WA

Emanuela Taioli, MD, PhD
Director, Institute for Translational Epidemiology
Icahn School of Medicine at Mount Sinai
New York, NY

Daniel Zelterman, PhD
Professor of Public Health (Biostatistics)
Department of Biostatistics
Yale School of Medicine
New Haven, CT

Luoping Zhang, PhD
Professor in Toxicology
School of Public Health
University of California, Berkeley
Berkeley, CA

TABLE OF ACRONYMS

ACRONYMS	DESCRIPTION
AAF	2-Acetylaminoflourene
AHS	Agricultural Health Study
AIDS	Acquired Immunodeficiency Syndrome
AOP	Adverse Outcome Pathway
ATS	Academy of Toxicological Sciences
BW	Body Weight
CASAC	Clean Air Science Advisory Committee
CDK	Cyclin-dependent kinase
CI	Confidence Interval
CNV	Gene Copy Number Variation
DABT	Diplomate of the American Board of Toxicology
DNA	Deoxyribonucleic Acid
EFSA	European Food Safety Authority
FACE	Fellow of the American College of Epidemiology
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act of 1996
FRSC	Fellow of the Royal Society of Chemistry
GM	Genetically Modified
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
IARC	International Agency for Research on Cancer
IP	Intraperitoneal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MM	Multiple Myeloma
MOA	Mode of Action
MRID	EPA OPP Master Record Identification Number
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OCSPP	EPA Office of Chemical Safety and Pollution Prevention

ACRONYMS	DESCRIPTION
OECD	Organization for Economic Cooperation and Development
OPP	Office of Pesticide Programs
OR	Odds Ratio
OSHA	Occupational Safety and Health Administration
RR	Relative Risk
SAP	FIFRA Scientific Advisory Panel
SAS	Statistical Analysis System
SCE	Sister Chromatid Exchanges
USDA	United States Department of Agriculture
US EPA or EPA	United States Environmental Protection Agency
WHO	World Health Organization
8-OH-dG	8-hydroxy-2' -deoxyguanosine

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed the meeting minutes and final report of the SAP meeting regarding scientific issues associated with **EPA's evaluation of the carcinogenic potential of glyphosate.** Advance notice of the SAP meeting was published in the *Federal Register* on July 26, 2016 (81 FR 48794).

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. Use of glyphosate in the United States and globally has increased over time, particularly with the introduction of glyphosate-resistant crops; however, usage has stabilized in recent years due to the increased number of weed species becoming resistant to glyphosate. Glyphosate is currently undergoing Registration Review, which is a program where all registered pesticides are reviewed at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act.

Recently, several international agencies have evaluated the carcinogenic potential of glyphosate. In March 2015, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), concluded that glyphosate was "probably carcinogenic to humans" (Group 2A). Later, in November 2015, the European Food Safety Authority (EFSA) concluded that glyphosate was unlikely to pose a carcinogenic hazard to humans. In May 2016, the Joint Food and Agriculture Organization (FAO) / WHO Meeting on Pesticide Residues (JMPR), another subdivision of the WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet.

Recently, EPA collected and analyzed a substantial amount of data informing the carcinogenic potential of glyphosate and utilized its draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment*" (EPA, 2010) to assess its potential carcinogenic hazard. The draft framework provides the foundation for evaluating multiple lines of scientific evidence and includes two key components: (i) Problem formulation and (ii) Use of the mode of action/adverse outcome pathway (MOA/AOP) frameworks. A comprehensive analysis of data on glyphosate from submitted guideline studies and the open literature was performed. This included epidemiological, animal carcinogenicity, genotoxicity, metabolism, and mechanistic studies. Guideline studies were collected for consideration from the toxicological databases for glyphosate and glyphosate salts. A fit-for-purpose systematic review was conducted to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate. Furthermore, the list of studies obtained from the toxicological databases and systematic review was cross-referenced with recent internal reviews, review articles from the open literature, and international agency evaluations (i.e., IARC, EFSA, and JMPR).

Available data from epidemiological, laboratory animal carcinogenicity, and genotoxicity studies were reviewed and evaluated for study quality and results to inform the human carcinogenic potential of glyphosate. Additionally, as described in the draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment*," the

multiple lines of evidence were integrated in a weight-of-evidence analysis using the modified Bradford Hill Criteria considering concepts such as strength of association, consistency of observations, dose response, temporal concordance, and biological plausibility.

The focus of this SAP meeting was on soliciting advice from the Panel on the evaluation and interpretation of the available data for each line of evidence and the weight-of-evidence analysis, as well as how the available data inform cancer classification descriptors per the Agency's 2005 *Guidelines for Carcinogen Risk Assessment*. The Agency's evaluation is summarized in an Issue Paper entitled: Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs, September 12, 2016 (EPA, 2016a).

During the FIFRA SAP meeting, US EPA personnel provided the following presentations (listed in order of presentation):

Welcome and Opening Remarks – Jack Housenger, Director, Office of Pesticide Programs

Introduction – Dana Vogel, Director, Health Effects Division, Office of Pesticide Programs

Overview of Glyphosate Registration and Carcinogenic Potential Evaluation – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Systematic Review and Data Collection Methods – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Epidemiology Studies – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Animal Carcinogenicity Studies – Anwar Dunbar, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Genetic Toxicity – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Integration and Weight-of-evidence Analysis Across Multiple Lines of Evidence – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

PUBLIC COMMENTS

Oral statements:

During the December 13-16, 2016 FIFRA SAP meeting, oral statements were provided by the following individuals and groups.

1) Daniele Court-Marques, MSPS, on behalf of the European Food Safety Authority (EFSA)

2) Lars Niemann, DVM, on behalf of the German Federal Institute for Risk Assessment (BfR)

3) Donna Farmer, PhD, Caroline Harris, PhD, John Acquavella, PhD, James Bus, PhD, Joe Haseman, PhD., David Kirkland, PhD, and Rick Reiss, PhD, on behalf of Monsanto Company

4) James S. Bus PhD, DABT, Fellow ATS, on behalf of Nufarm Americas Inc.

5) Amechi Chukwudebe, PhD, on behalf of BASF Corporation

6) James S. Bus PhD, DABT, Fellow ATS, and Steven Levine, PhD, on behalf of CropLife America

7) Deborah Hommer, on behalf of Virginians for Medical Freedom

8) Scott Slaughter, on behalf of the Center for Regulatory Effectiveness

9) Sabitha Papineni, PhD, on behalf of Dow AgroSciences

10) Jacob Vukich, PhD, on behalf of DuPont Crop Protection

11) Kevin Hoyer, on behalf of the American Soybean Association

12) Andy Hedgecock, on behalf of FMC Corporation

13) Martin Barbre, on behalf of the National Corn Growers Association

14) Amanda Starbuck, on behalf of Food and Water Watch

15) Bill Freese, on behalf of the Center for Food Safety

16) Robert Hamilton, PhD, on behalf of Sumitomo Chemical

17) Montague Dixon, on behalf of Syngenta Crop Protection

18) Michael Hansen, PhD, on behalf of Consumers Union

19) Sheryl H. Kunickis, PhD, on behalf of the US Department of Agriculture

20) Laura E. Mayer, Marghi Barnes, and Kathy Blum, on behalf of Moms Across America

21) Reverend Billy Talen and Ms. Robin Laverne Wilson, on behalf of The Immediate Life Church

22) Nichelle Harriott, PhD, on behalf of Beyond Pesticides

23) Dalia Hashad, PhD, on behalf of Avaaz

24) Peter Infante, DDS, DrPH, FACE, on behalf of himself

25) David Spak, on behalf of Bayer Crop Science

26) Alexis Baden-Mayer, Esq., on behalf of the Organic Consumers Association

27) Luther Markwart, on behalf of the American Sugarbeet Growers Association

28) James Barile, on behalf of the Natural Resources Defense Council

Handouts provided by oral presenters are available in the public docket at https://www.regulations.gov, docket number EPA-HQ-OPP-2016-0385.

Written statements:

Numerous written public comments were submitted to the FIFRA SAP for the December 13-16, 2016 meeting on EPA's evaluation of the carcinogenic potential of glyphosate. These documents are contained in over 350 docket entries and represent the comments of over 260,000 individuals. These comments are available in the public docket at https://www.regulations.gov, docket number EPA-HQ-OPP-2016-0385. Appendix 1 contains a summary list of these docket entries.

EXECUTIVE SUMMARY

US EPA presented a set of charge questions to the FIFRA SAP covering five broad aspects of the Agency's evaluation of the carcinogenic potential of glyphosate. The questions centered on:

1) the completeness, transparency, and appropriateness of the Agency's methods to collect references for the evaluation;

2) the epidemiological studies investigating the potential for associations between glyphosate exposure and cancer outcomes;

3) the laboratory rodent carcinogenicity studies for glyphosate;

4) assays investigating the genotoxic potential of glyphosate; and

5) the completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate for humans.

The completeness, transparency, and appropriateness of the Agency's methods to collect references for the evaluation

The Panel found that EPA's literature review methods were in general transparent and appropriate. However, the Panel provided several recommendations for updated searches that would be more inclusive and capture more recent, relevant publications. In addition, the Panel recommended that the Issue Paper identify and discuss any rodent cancer bioassays of glyphosate-based formulations. Some members of the Panel proposed that searches of "glyphosate and immunotoxicity" and "non-Hodgkin's lymphoma (NHL) and farming" might be informative. Further, some members of the Panel noted that, since most of the glyphosate in commerce in the U.S. is supplied as the isopropylamine salt, it would be of interest to review whether isopropylamine *per se* or the glyphosate isoproylamine combination has been tested for carcinogenicity, mutagenicity, and immunotoxicity.

Given the importance of epidemiologic data generated by the Agricultural Health Study (AHS), the Panel recommended that EPA contact the AHS investigators to determine whether updated data on incidence of non-Hodgkin's lymphoma (NHL) and other cancers are available. As was discussed at length during the Panel's deliberations, the relevant AHS publication (De Roos et al., 2005) has a limited follow-up period, and so is less informative than it might be were additional and more recent data from this important study-cohort available.

One Panel member was concerned with regard to the sensitivity of the review process. The unusually low number of epidemiological studies identified through searches of PubMed.gov, Science Direct®, and Web of Science™ may indicate that EPA needs to utilize more comprehensive and sensitive techniques in conducting searches of the databases than has been employed to date. It is nonetheless likely that the Agency did identify all of the relevant papers by the combined methods of computerized searching and other means (such as from the reference lists of other relevant papers and reviews).

Some Panel members noted that it is important for the study selection process to involve multiple people independently selecting studies, scoring studies, and then to have a process to reach consensus regarding the selected studies. It was noted that this aspect of the process was not clearly described in the Issue Paper.

Several Panel members noted that it would have been helpful if the Issue Paper had been easier to review. For EPA's Clean Air Science Advisory Committee (CASAC), the Agency produces technical documents for review with references linked using HERONET, a database which provides access to full scientific articles. A Panel member suggested that the Agency do the same for FIFRA-related Issue Papers.

The epidemiological studies investigating the potential for an association between glyphosate exposure and cancer outcomes

The Panel concluded that, overall, the Agency's review and evaluation chose relevant epidemiology studies that inform the assessment of the human carcinogenic potential of glyphosate. The Panel noted that EPA's continuing effort to incorporate human data into risk assessment is commendable. The Panel also found that EPA's evaluation of the epidemiologic studies used a sound, appropriate and acceptable approach, although how the individual study rankings were judged and ultimately how the final rankings incorporating subgroup rankings were determined were not always evident to the Panel without the Agency's explanation. In addition, some Panel members were concerned that important issues that affect the quality ranking of the Agricultural Health Study were not considered. The Panel observed that the agency correctly addressed the issue of both case-control and cohort studies having adequate latency periods as a validity criterion, and pointed out the difficulty of addressing this issue in the absence of reliable data on latency periods for the cancers of interest. However, Panelists had different opinions about the importance of considerations of latency in interpreting epidemiology results.

The Panel recommended that the concept of realized study design should be incorporated into the evaluation of study design. In addition, some Panel members suggested that it may be useful to adopt a classification criterion that separates studies by their 1) design, 2) implementation (which includes consideration of issues such as attempts at full enrollment, completeness of questionnaire design, and completeness of collection of other data) and 3) data analyses characteristics.

Panel members agreed that based on the evidence presented in the Issue Paper (EPA, 2016a), Tables 3.3 and 3.4, there is no reliable evidence of an association between glyphosate exposure and any solid tumor, or between glyphosate exposure and leukemia or Hodgkin's lymphoma, even if the possibility that some of the studies reviewed were subject to potential biases is ignored (such as recall or measurement error bias). However, some Panel members also noted that the epidemiologic data are still limited, and that *none* of the studies is of glyphosate manufacturing workers or others who may be relatively highly exposed. This was felt to be a critical data-gap.

The Panel also agreed with EPA that available studies do not link glyphosate exposure to multiple myeloma (MM). However, one Panel member noted that a recently published meta-

analysis (Chang and Delzell, 2016) reported a meta-estimate of the relative risk for the association between MM and glyphosate of 1.4 (with 95% CI of 1.0-1.9). Another panel member, however, noted that to the extent that the primary study results may be biased high, the meta-statistic will be similarly biased high.

Some Panel members supported the Agency conclusion that "the association between glyphosate exposure and risk of NHL cannot be determined based on the available data," although for somewhat different reasons than provided by EPA. These Panelists believe that all the significant findings from three of five case-control studies and three meta-analyses were most likely a result of recall and other potential biases. Furthermore, the only study not subject to recall bias, the prospective cohort study (De Roos et al. 2005), did not show statistical evidence of a positive association.

Some Panel members emphasized that, as EPA itself has estimated, all available epidemiologic studies of glyphosate-users are not really studies of glyphosate over-exposed workers. These Panel members believe this is a crucial point, and one more reason to doubt that the weakly positive NHL case-control study results are indicative of any genuine biological response due to glyphosate -- as opposed to countless other chemical, biological, microbiological, and antigenic factors associated with living or working on a farm. These Panel members noted that many epidemiological studies have reported farmers to be at increased risk of lymphoma (and sometimes leukemia), including decades before glyphosate was used. One Panel member expanded on this noting that while the Agency correctly considered whether studies had adjusted for exposure to other individual pesticides as one of the important criteria for quality assessment, it has not considered the equally important exposure to farm animals (cattle, pigs, sheep, poultry, etc.) that also needs to be adjusted for in determining the quality of epidemiological studies. These animal exposures involve exposure to oncogenic viruses present in the animals, and also to immune system stimulant endotoxins that are particularly of relevance for tumors of the hematopoietic and lymphatic systems, especially as their occurrences predate the introduction of glyphosate and some of the studies reviewed did show them as important risk factors.

Other Panel members disagreed with the Agency's conclusion, emphasizing the value and importance of the findings reported from several dose-response analyses and meta-analyses. These Panelists noted several considerations including that while the majority of the individual studies are not statistically significant, combining the results using meta-analysis shows a scientifically important and statistically significant elevated NHL risk that is relevant for understanding carcinogenic potential. It appeared to some Panel members that the Agency did not fully consider that the data could be suggestive of a lymphomagenic effect of glyphosate. In particular, some Panel members felt that EPA's discussion of the epidemiological evidence appeared to discount statistical findings and overemphasize non-statistical criteria. Thus, some Panel members believed that there is limited but suggestive evidence of a positive association between glyphosate exposure and risk of NHL. These panelists recommended that the Agency revise their conclusion to something along the lines of the following:

"Based on the weight-of-evidence from epidemiological studies and meta-analyses, the Agency cannot exclude the possibility that observed positive associations between glyphosate

exposure and risk of NHL suggest human carcinogenic potential of glyphosate, even though study limitations and concerns about potential biases remain."

Other Panel members, however, strongly disagreed with such a statement; they instead agreed with EPA that the positive associations with glyphosate reported in some retrospective case-control studies of NHL are (i) too weak and (ii) too likely to be confounded by other aspects of living or working on a farm to be properly considered even as suggestive – especially given the null results in the only available prospective cohort study of pesticide applicators. These panelists noted that if the reported odds-ratios and/or relative risks were instead (i) larger and more precise, and (ii) for some solid tumor-type not otherwise known to appear in excess in farmers, then they would be more persuaded that glyphosate possibly posed a cancer-risk. They also noted that if glyphosate, at the very small exposure levels actually received by farmers, were a bona fide human carcinogen, then the toxic potency of glyphosate in humans would have to be on the order of 100,000 times larger than it has proven to be in numerous studies using laboratory rodents. These panelists knew of no precedent for such a discrepancy – especially for a compound, such as glyphosate, that is (i) poorly absorbed, (ii) non-reactive *per se*, and (iii) not converted *in vivo* to reactive metabolites.

Panel members noted that workers in companies that manufacture, formulate, or handle and sell glyphosate on a wholesale basis comprise a promising resource for epidemiologic study that should be investigated. One panel member noted that there are at least 15 companies that have registered glyphosate products with EPA and suggested that it is likely that large numbers of exposed workers (perhaps many more than those directly involved in manufacturing glyphosate) could be identified for cohort studies in companies involved in the formulation or wholesale handling and sale of glyphosate.

The Panel also provided comments and recommendations regarding the specific criteria including study design, study power, statistical analysis, confounding, statistical bias, recall and selection bias. The Panel discussed at length the possibility that recall bias in retrospective case-control studies can result in over-estimation of the risk of NHL associated with pesticide exposure. Some Panel members felt that key studies show evidence of recall bias, exacerbated in some cases by selection bias, and therefore these studies are not reliable for evaluating the carcinogenicity of glyphosate. Other panel members felt that the necessary data to appropriately evaluate whether recall bias is present or not in the reviewed studies are not available and, in any case, the potential for important impacts of recall bias on the findings could not be reliably separated from those of other potential biases. Another Panel member noted, however, that use of proxy respondents (as necessitated in all retrospective case-control studies when cases are deceased) has been shown to bias cancer risk-estimates above the null (sometimes substantially so), both for pesticides in general and for glyphosate in particular.

The laboratory animal carcinogenicity studies for glyphosate

EPA reviewed and analyzed the results of 15 rodent bioassays and concluded that the results as a whole do not indicate carcinogenicity of glyphosate. Some Panel members agreed with this conclusion, noting that the Issue Paper correctly finds the tumor-response data to be too inconsistent to be considered compound-related. Other Panel members interpreted the totality of the tumor data as supporting the hypothesis that glyphosate may cause the promotion or

progression of common spontaneous lesions. These Panel members argued that there is sufficient evidence to conclude that glyphosate is a weak rodent carcinogen and/or tumor promoter. The Panel noted that holistically interpreting results from 15 rodent cancer bioassays posed a unique challenge.

Overall, the Panel was divided with regard to its interpretation of apparently conflicting evidence from the rodent bioassays of glyphosate. Some Panel members pointed out that true carcinogenic responses should be reproducible, and that the estimated positive results in some of the rodent bioassays of glyphosate were likely to be false positives. These Panelists focused on the lack of consistency among the responses across the entire, unusually large glyphosate database, and the fact that the number of significantly positive results in this large database was no greater than would be expected from random assignment of animals to dose groups. These Panelists also noted EPA's weight-of-evidence ignored the serious multiple comparison problem caused by focusing attention on the most extreme tumor responses without also explicitly noting the many negative dose-response relationships and other null results.

Some Panel members felt that the Agency's weight-of-evidence evaluation gave excessive weight to several factors, including lack of monotonic dose response relationships, historical tumor rates, lack of statistical significance in pair-wise comparisons when there is a significant positive trend, and discounting results at exposures greater than the "limit dose" of 1,000 mg/kg/day. Panelists who disagreed with the Agency's conclusions noted there was considerable heterogeneity between studies that needed to be taken into account. They recommended pooled analyses of multiple studies, within endpoint, gender, and species, as a valid approach to distill the evidence from multiple studies. In support of their conclusion they cited an example, provided in the public comments, of pooled analyses of several endpoints for most of the mouse studies.

Some Panel members felt that the Agency's discounting of statistically-significant trends based on the idea that they were not monotonically increasing was flawed. The Panel noted that a monotonic dose response relationship is not a criterion for a positive rodent response in the Agency's 2005 *Guidelines for Carcinogen Risk Assessment*.

Overall, the Panel concluded that the EPA evaluation does not appear to follow the EPA (2005) *Cancer Guidelines* in several ways, notably for use of historical control data and statistical testing requirements. Regarding historical controls, the Panel noted that the default position should be to *not* rely on historical control data except when concurrent controls yield clearly unreliable results. The Panel recommended that EPA articulate why historical control data were incorporated into some of its analyses and not in others. Regarding statistical testing requirements, the Panel noted that requiring a significant pairwise comparison corrected for the number of pair-wise tests in addition to a significant trend is neither consistent with the 2005 *Guidelines for Carcinogen Risk Assessment* nor a conservative approach for public health protection.

In the view of some Panel members, there are sufficient data to conclude glyphosate is a rodent carcinogen using the approaches recommended to interpret the biological significance of tumor responses in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*. However, other Panel members strongly disagreed with this conclusion finding no reliable and consistent

evidence that glyphosate induces or promotes tumors in laboratory rodents. Some Panel members also did not agree that applying a "conservative test" is necessarily an appropriate scientific goal when evaluating the potential carcinogenicity of glyphosate. Instead these Panel members recommended the standard scientific approach be followed whenever feasible (e.g., apply a decision rule that has a false positive rate equal to the standard rate of 5%).

The Panel concluded that the EPA needs to clarify its position on results from exposures that exceed 1,000 mg/kg/day (the limit dose). Panel members differed regarding the relevance and use of results above the "limit dose" for determining the carcinogenic potential of glyphosate for humans. Some Panel members felt that at high doses homeostatic mechanisms could be overwhelmed, so that results might not be relevant for the much lower levels of exposure experienced by people. Other Panelists noted that since glyphosate is so non-toxic, results at dose-rates that are several-fold larger than the limit dose of 1,000 mg/kg/day could indeed be relevant -- since such doses were still smaller than the maximally tolerated dose. Based on EPA (2005) *Cancer Guidelines*, some members of the Panel concluded it is questionable whether results from exposures greater than 1,000 mg/kg/day, but less than doses corresponding to 5% in diet, should be given less weight. Many members of the Panel concluded not considering or discounting tumor responses at doses that exceed 1,000/mg/kg/day is not consistent with either EPA (2005) *Cancer Guidelines* or standard ways in which bioassay results are typically interpreted. They noted that the limit dose is included in the *guidelines* as a design criterion and it is not advisable to exclude observed data *post hoc* from the analysis and interpretation of experimental results.

Some Panel members agreed that it is important to control for multiple comparisons as described in the EPA *Guidelines for Carcinogen Risk Assessment* (a point noted in public comments as well), but felt that the Agency's specific technique for making this adjustment was flawed. These panelists made specific recommendations for improvements in the analysis.

Other Panelists felt that a multiple comparisons adjustment was not appropriate for addressing the question of whether glyphosate has carcinogenic potential, asserting instead that compelling evidence of carcinogenicity for any tumor-type, regardless of replicability, suffices. These panelists felt that the appropriate method for combining evidence from multiple studies is to use pooled analysis or meta-analytical tools.

Some Panel members believed that differences in study designs could explain some of the tumor response discrepancies, and that, overall, the rodent bioassay data were consistent with glyphosate acting as a weak tumor promoter. There has been no direct test of this hypothesis (such as in a standard initiation-promotion bioassay), and therefore other Panel members felt that such a conclusion was speculative and ignored the lack of reproducibility.

Assays investigating the genotoxic potential of glyphosate

Panel members found that the Agency's overall weight-of-evidence and conclusion that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route are sound. Areas of remaining uncertainty are related to the potential for glyphosate-induced inflammation and genotoxic effects secondary to toxicity caused by high dose exposures (i.e., glyphosate-induced inflammation, oxidative stress, 8-OH-dG, and sister chromatid exchanges or

SCE) and whether the glyphosate-containing formulations have genotoxic potential. In addition, one Panel member noted that none of the assays employed provides an unbiased (global) measure of small insertions, deletions and rearrangements, which can result in gene copy number variation (CNV) and recommended that this section of the Issue Paper be expanded to address this point.

Panel members agreed that the review and evaluation process of genotoxicity studies is sufficient given the limits of the available assays, which are described in the report (first paragraph of section 5.1) as being sufficient to detect: "1) changes in single base pairs, partial, single or multiple genes, or chromosomes, 2) breaks in chromosomes that result in transmissible deletion, duplication or rearrangement of chromosome segments, and 3) mitotic recombination."

Panel members also agreed that, in the determination of whether glyphosate is likely to be genotoxic in humans, the EPA document focuses appropriately on studies conducted in cultured mammalian cells and laboratory animal models.

One Panel member encouraged the agency to consider two key human biomonitoring studies in their evaluation of genotoxicity, specifically studies by Bolognesi et al. (2009) and Koureas et al. (2014).

A few Panel members commented that if glyphosate causes progression of spontaneously arising lesions (in cells carrying cancer driver mutations or other types of DNA damage), then humans may be at risk of glyphosate-induced carcinogenicity, and the longer human lifespan (as compared to rodents) is expected to contribute to the risk. Other members felt that such concerns were speculative.

The completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate

The Panel was asked to comment on the completeness, transparency, and scientific quality of the Agency's characterization of the carcinogenic potential of glyphosate as presented in the Issue Paper, paying attention to how the Agency uses the modified Bradford Hill criteria of strength of association, consistency, dose response, temporal concordance, and biological plausibility in its assessment.

The Panel noted that the conclusion on glyphosate carcinogenicity offered in the Issue Paper has two parts. The first part is a hazard statement while the second part is a risk characterization statement. Since the Issue Paper is not a full risk assessment of technical glyphosate as outlined in the 2005 *Guidelines for Carcinogen Risk Assessment*, the Issue Paper conclusion was assessed by the Panel as a hazard statement.

Completeness: The Panel concluded that the Issue Paper represents a comprehensive review of the available epidemiologic data, laboratory animal bioassay data, and genotoxicity data, but also noted some limitations.

First, the epidemiologic data reviewed in the Issue Paper are limited to users of glyphosate-based herbicides (such as farmers and other herbicide-applicators), but, as EPA estimates, exposures are fairly low – 0.03-7 mg/kg/day for the most highly exposed workers. Published

studies of potentially more highly exposed workers, such as those who manufacture, formulate or are involved in the wholesale handling or selling of glyphosate, are apparently not available.

Second, because the central epidemiologic question with regard to glyphosate is whether its use is associated with risk of developing non-Hodgkin's lymphoma (NHL), some Panel members felt that the Issue Paper would benefit from a broader review of NHL risk-factors that have long been associated with farming.

Third, the Issue Paper does not present potentially relevant data on isopropylamine, despite the fact that most glyphosate in use is as the isopropylamine salt.

Transparency: The Panel found the Issue Paper to be reasonably transparent, although concern was expressed that some of the documents and data used by EPA in this assessment require special procedures for access and a few studies were not available to the Panel or the public. The Agency explained that FIFRA regulations are responsible for some of these limitations. Regardless, the Panel questioned whether the public could fully review and reproduce the conclusions reached by EPA.

Scientific quality: The Panel felt that the scientific quality of the Issue Paper could be improved. Some Panel members pointed to insufficient study design details, incomplete discussions of data limitations, and use of assessment criteria that do not follow EPA (2005) *Cancer Guidelines*. Panel members noted that the health-effects database on glyphosate (from both toxicological and epidemiological studies) poses a somewhat unique challenge, but that the Agency could nonetheless improve upon the scientific quality of its weight-of-evidence approach. For example, several Panel members, and several public commenters, presented methods for formally and holistically assessing the results from the 15 or so laboratory rodent bioassays of glyphosate acid or glyphosate salts that could improve the Agency's approach.

Dose-response and temporal concordance (Bradford Hill Criteria): A number of Panel members did not agree with how the Issue Paper weighed the epidemiological study findings, particularly for NHL, and were skeptical of the report's arguments leading to its conclusion of "no observed association." Not all Panel members agreed with the Issue Paper's conclusion that findings in rodent bioassays are not treatment-related. There was disagreement among the Panel members regarding which analyses/results constituted a significant finding and which instead were false positives. Some panelists disagreed with EPA's assertion that monotonically increasing dose-response relationships were required in order for responses to be considered to be compound-related, and felt that the Agency could better explain its reliance on tumor responses in historical, as opposed to concurrent, control groups. The Panel's consensus was that the Issue Paper needs to refine and strengthen its arguments regarding the weight assigned to "limit dose" responses in the bioassays. The Panel agreed with the Issue Paper's conclusions regarding the lack of genotoxicity effects of glyphosate.

Strength, consistency, and specificity (Bradford Hill Criteria): With regard to the epidemiologic findings, the Panel concurred with the Issue Paper's conclusions regarding solid tumors, leukemia, multiple myeloma and Hodgkin's lymphoma, but differed in their agreement with the Issue Paper's conclusions of no reliable relationship between glyphosate exposure and NHL. The roles and impacts of recall bias, selection bias, residual confounding by other farm

exposures, and reliability of the meta-analyses were all points of disagreement. Several Panel members noted that the epidemiologic database is *unusually uninformative*, in that (i) glyphosate based herbicide-users are not exposed to doses much larger than those ingested by many consumers via their diets, and (ii) the cancer-type that is weakly associated with glyphosate – NHL – has also been linked with farming for many decades, including before use of this herbicide.

The Panel discussed at length the consistency, or lack thereof, of the laboratory rodent bioassay results. Some Panel members suggest that in evaluating the data from the rodent bioassays, dose-response modeling in a pooled analysis would provide a better basis for assessing the consistency and implications of the bioassay results. The current draft instead focuses on each bioassay individually, which obscures readers' abilities to judge whether results are consistent and likely to be compound-related.

Biological plausibility and coherence (Bradford Hill Criteria): Some Panel members felt that the Issue Paper would benefit from a discussion of the hypothesis that glyphosate may be a weak cancer promoter and to explore the immunotoxicity of glyphosate; though not all Panel members felt that having a biologically plausible MOA is a necessary condition to classifying a substance as a carcinogen, as implied in the Issue Paper. The discussion should consider observations of glyphosate treatment-related increases in frequently occurring spontaneous tumors noted in primary study documents (Knezevich and Hogan 1983, Wood 2009b), observations of treatment-related decreases in pre-neoplastic lesions concurrent with increases in tumor frequency in the same organ (Lankas 1981, Knezevich and Hogan, 1983), and significant increases in malignant tumors of treated male rats relative to controls across tumor sites (Atkinson 1993a), which suggest glyphosate may cause promotion or progression of spontaneous pre-neoplastic lesions (also see response to Charge Question 3d).

Uncertainty (Bradford Hill Criterion): The Panel concluded that uncertainties in epidemiological and animal study evidence are well discussed in appropriate sections of the Issue Paper. Uncertainties identified in earlier sections of the Issue Paper, such as excluding formulations with glyphosate and the limitations regarding available pharmacokinetics data, should be expanded upon. Some Panel members noted that in the discussion of the epidemiology findings, the Issue Paper does not adequately assess the likely impacts of potential biases (such as recall and selection) and residual confounding on the odds ratio estimates or the problems that could bias the estimates obtained from the currently available results of the Agricultural Health Study.

Evaluation and Proposed Conclusion: Using a weight-of-evidence approach, the Issue Paper concludes that glyphosate is "not likely to be carcinogenic to humans," especially at reasonably foreseeable dose-rates. Some Panel members agreed with this characterization, while other Panel members felt that the better descriptor for glyphosate is "suggestive evidence of carcinogenic potential." Many Panelists noted that crucial data were equivocal, and that additional data on cancer morbidity and/or mortality from studies of glyphosate-exposed workers would be desirable.

Glyphosate/Tox

Caswell file

40

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

004370

WASHINGTON, D.C. 20460

MEMORANDUM APR 3 1985

Reasonable Glyphosate

SUBJECT: Glyphosate; ~~EPA~~ Reg.#: 524-308; mouse oncogenicity study
Caswell #: 661A
Accession #: 251007-014

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
Product Manager (25)
Registration Division

4/1/85

THUR: Robert P. ~~Zendzian~~, Ph.D.
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 3/29/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

Hfn cw HB 4/2/85

Conclusions:

1. Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The study is acceptable as core-minimum data.

2. The information on the oncogenicity of glyphosate was evaluated by a Toxicology Branch AD Hoc Committee which concluded that this was an oncogenic response. A copy of the consensus report of the committee is attached.

Review:

1. A chronic feeding study of Glyphosate in mice (Biodynamics # BDN-77-420; Project No. 77-2061; 7/21/83).

Test Material:

Glyphosate technical, purity = 99.7%; fine, white clumped powder; lot number, NB178260813; NB178261017.

Groups of 50 male and 50 female randomized CD-1 mice, individually caged, were administered diets containing 0, 1000, 5000, and 30,000 ppm of test material for 24 months.

Parameters evaluated were toxic signs, mortality, body weight, food consumption, water consumption and hematology at 12, 18 and 24 months.

All animals were necropsied and selected organs were weighed. Tissues were stained in H and E and examined microscopically.

Statistical analyses of the data were performed.

Results:

No treatment-related toxic signs were noted during the study. Mortality was low during the first 18 months of the study as shown in the table below as reported:

Cumulative Mortality

DOSE	Males			Females		
(ppm)	12 Mo	18 Mo	24 Mo	12 Mo	18 Mo	24 Mo
0	9	12	30	3	15	30
1,000	9	19	34	4	16	38
5,000	7	14	33	1	8	23
30,000	4	11	24	5	13	27

Body weight was consistently decreased for males and to a lesser extent, females at the 30,000 ppm dosage level during the study at several sampling intervals. Changes in body weight at the low- and mid-dose group were variable and not dose-related.

Food consumption showed no compound-related or dose-related effect. Hematological values although significant in some instances did not show a consistent dose-related response.

Necropsy did not show treatement-related lesions. There was good correlation between gross and microscopic findings. The relative and absolute weight of the testes and ovaries were increased in high dose males and females, but no histopathological finding was present as a underlying factor.

Renal tubule adenomas occurred in male mice in the following manner as reported:

Dose (ppm)	0	1,000	5,000	30,000
Number examined	49	49	50	50
Renal tubule adenoma	0	0	1	3

004370

They occurred in male mice 4029, 4032 and 4041 of the high-dose, and male 3023 of the mid-dose group and all were unilateral.

These tumors are rare, dose related and considered compound-related. These tumors were present at terminal kill.

Other neoplasmas were considered unrelated to treatment. No effect on latency was noted.

Significant trends and significant high-dose effects were observed in non-neoplastic lesions. The lesions considered treatment-related were hepatocyte hypertrophy, central lobular hepatocyte necrosis and chronic interstitial nephritis in high-dose males and proximal tubule epithelial basophilia and hypertrophy in high-dose females.

The table below shows the incidence of these lesions as reported:

	Control	Low	Mid	High	Linear Trend
Central lobular hepatocyte hypertrophy					
- males	9/49	5/50	3/50	17/50	b
- females	3/49	5/50	5/50	1/49	
Central lobular hepatocyte necrosis					
- males	0/49	2/50	2/50	10/50[a]	b
- females	2/49	1/50	4/49	2/49	
Chronic interstitial nephritis					
- males	5/49	2/49	7/50	12/50	b
- females	4/50	8/50	2/50	4/50	
Proximal tubule epithelial basophilia and hypertrophy					
- males	15/49	10/49	15/50	7/50	
- females	0/50	2/50	4/50	9/50[a]	a

[a]Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-Square test (uncorrected for continuity).

[b]Statistically significant linear trend ($p \leq 0.01$) using the Cochran-Armitage test.

Conclusion:

Glyphosate was oncogenic in male mice producing a dose-related increased in renal tubule adenomas, a rare tumor. Dose-related non-neoplastic lesions occurred in both sexes. The NOEL for systemic effects was 5000 ppm. At the LEL, 30,000 ppm, there were increased hepatocyte hypertrophy, hepatocyte necrosis and interstitial nephritis in male mice and an increased incidence of proximal tubule epithelial basophilia and hypertrophy in female mice. Additionally, there were decreased body weights in male and female mice at 30,000 ppm which are considered compound-related.

Classification:

Core minimum data.

Glyphosate / Tox

(44)

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004855
Releasable

DEC 12 1985

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. #: 524-308; Roundup; Glyphosate; Pathology Report on Additional Kidney Sections
Caswell No. 661A
Accession No. 259621

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

THRU: Robert P. Zendzian, Ph.D. 12/12/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 12/12/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

12/12/85

Requested Action:

Review pathology report on additional kidney sections.

Background:

Glyphosate was considered oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The incidence of this tumor was 0, 0, 1, and 3 in the control, low-, mid-, and high-dose groups, respectively.

Additional evaluation of all original renal sections identified a small renal tubular adenoma in one control male (animal No. 1028) which was not diagnosed as such in the original pathology report.

Subsequently, Toxicology Branch recommended that additional renal sections be cut and evaluated from all control and glyphosate treated male mice.

This review contains the evaluation of the submitted results of the additional sectioning and pathological data.

Conclusion:

The results of the additional pathological evaluation on re-cut kidney sections in male mice demonstrated no additional tumors were present. The significance of this finding will be determined later by the Ad Hoc committee.

Review:

1. The pathology report of additional kidney sections submitted by the registrant (Monsanto) showed that the renal tubule adenoma incidence in male mice was as follows:

Dose (ppm)	0	1000	5000	30,000
Animal number			3023	4029,4032,4041
Renal tubule adenoma	0	0	1	3
No. examined	49	49	50	50

The additional tumor in the control group which had been diagnosed from the re-evaluation of the original slides was not present in the re-cut kidney sections.

Toxicology Branch's pathologist (report attached) stated that the control tumor "does not represent a pathophyioloically significant change".

Statistical analysis of the tumor results showed no significant ($P<0.05$) difference in the incidence of renal tubule adenoma between control and treated groups.

However, the test for linear trend in proportions resulted in a $p=0.016$ which is statistically significant.

According to the registrant's pathology report, non-neoplastic kidney lesions did not reveal evidence of an ongoing chemically induced neprotoxicity.

Based on the original report and the new report, Toxicology Branch concludes that chronic interstitial nephritis occurred in compound-related manner in males at the high-dose as is shown below:

	Males (Chronic Interstitial Nephritis)			
Dose (ppm)	0	1000	5000	30,000
Incidence				
Original report	5/49	2/49	7/50	12/50
New report	5/49	1/49	7/50	16/50

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

006541

JAN - 5 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - Monsanto Comments to Glyphosate Guidance Document

Caswell No.: 661A
TOX Br. Proj. No.: 7-0773
Record No.: 197157-197162

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769C)

William Dykstra 12/18/87

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

and

Theodore M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Theodore M. Farber 12/28/87

Requested Action

Review Monsanto's comments relative to Glyphosate Guidance Document (Registration Standard). Monsanto specifically requests a waiver of the inhalation LC_{50} with glyphosate and a waiver of a repeat mouse oncogenicity study with glyphosate.

Conclusions and Recommendations

1. TB concurs with Monsanto's waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

EXHIBIT
38
1-23-19 MA
PENDLEY REPORTING

006541

2. TB does not concur with Monsanto regarding the waiver of the repeat mouse oncogenicity study (see discussion in review section).

TB requires that the mouse oncogenicity study be repeated in males only, using larger numbers of animals for each dose level to increase the statistical power of the bioassay. Possibly 200 mice per group may be needed.

For the repeat study the HDT should be 30,000 ppm since, at that dose level, the "equivocal" increase in kidney tumors was observed in the previous study. Additional doses of 15,000 and 7500 ppm are also recommended, which may provide an indication of a possible dose-response relationship.

Other experimental variables should be the same, as much as possible, as the previous mouse oncogenicity study.

A "tier approach" to histopathological examination of tissues/organs will be acceptable. Specifically, sections of kidney and liver should be examined from all high dosage level and control animals. In addition, all grossly observed findings suggestive of possible tumors should also be examined from all animals in all groups in the study. If the above examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should provide a protocol of the repeat study before the experimental work is initiated.

006541

Review

Issue Number I: Acute Inhalation LC_{50} Study With Glyphosate

In the Glyphosate Guidance Document, EPA stated that an acute inhalation study with glyphosate technical has not been submitted and is required.

Monsanto's Response

"There appears to be no justification for an acute inhalation study with glyphosate because: (a) People are not exposed to glyphosate. If any exposure does occur, it is either to the isopropylamine or sodium sesqui salts of glyphosate. Adequate inhalation toxicity studies have been or are being conducted with these end-use materials. The results of available studies indicate a relatively low degree of acute inhalation toxicity; (b) glyphosate is a nonvolatile solid material which is handled in manufacture as a wet cake (10-15% moisture) which precludes any inhalation exposure. We therefore request the Agency concur with Monsanto's opinion that this acute inhalation study is not required per Section 158.135, 81-3 Guidelines since glyphosate is not an inhalable material."

TB Conclusion and Recommendation

TB concurs with the Monsanto waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

Issue Number II: Repeat of the Mouse Oncogenicity Study

In the Glyphosate Guidance Document, the Agency requested a repeat of the chronic feeding/oncogenicity study in mice to fully address the question of ". . . whether the apparent effects noted in the mouse study (renal tubular adenomas) are biologically relevant."

Monsanto's Response

"The results of the mouse bioassay do not provide positive, or even suggestive, evidence of carcinogenicity. The most that can be said is that the results were equivocal as, in fact, the Scientific Advisory Panel stated. Furthermore, the SAP pointed out the fact that this equivocal finding occurred only at a dose level that exceeded the MTD. Quoting from the SAP report, '. . . no oncogenic effect is demonstrated using concurrent controls' and '. . . the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.'

006541

There appears to be no justification for requiring the repeat of a study with equivocal findings at a single site, only at dosage levels exceeding the MTD."

"Several expert toxicologists intimately familiar with the glyphosate chronic/oncogenic mouse study results, and personally involved in the SAP hearing on this issue, were asked to evaluate the need for a repeat study. All experts agreed that additional testing is not justified since the current study was conducted at levels exceeding the MTD and failed to demonstrate a treatment-related oncogenic effect. Their evaluations are enclosed in this part."

"As discussed previously, the fact Monsanto has agreed to repeat the chronic/oncogenic rat study with glyphosate diminishes even further the justification for a repeat mouse study."

"The results of the current rat and mouse studies, along with results to be obtained from a repeat rat study, should be sufficient to assess the oncogenic potential of glyphosate. A repeat mouse study is not necessary."

"Finally, based upon a review of the principles expressed in the Agency's draft 'Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies,' it is clear that the chronic/oncogenic mouse study was conducted at dosage levels which greatly exceeded the upper limit of 7000 ppm required for mouse studies. Furthermore, none of the requirements listed in that document which would necessitate a study are fulfilled for the mouse study (see Attachment 1)."

TB Conclusion and Recommendations

Regarding the need to repeat the mouse oncogenicity study with glyphosate, TB fully concurs with the conclusion and recommendation of the Scientific Advisory Panel (SAP) viz "The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions." In view of the equivocal oncogenic response in the first mouse study, TB believes the oncogenic potential of glyphosate in mice still remains unresolved and that a repeat mouse study is necessary to fully and adequately assess this potential.

TB would also point out that the "Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies," referred to by Monsanto, is a discussion of general principles that may be useful in the interpretation of oncogenic studies and as an aid in determining the need to repeat studies. As such, it is intended to provide guidance rather than rigid rules.

006541

When the circumstances of a particular situation indicate a strict application of the document may be inappropriate, TB will give precedence to what it believes is most prudent for the specific case at hand.

In the case of glyphosate it is recommended that the mouse oncogenicity study be repeated and that the highest dosage level tested be 30,000 ppm, as in the first study, rather than 7000 ppm (or 1000 mg/kg/day) as "suggested" in the MTD document. This dosage level requirement is being imposed to clarify the equivocal results observed at this same dosage level in the first study and in so doing to assess the full potential of glyphosate to induce tumors in mice. It is noted that at this dosage level (30,000 ppm) in the first mouse study, survival of male mice at 24 months was increased compared to male control mice; therefore, this dosage level is not a life-shortening level. It is also recommended that the mid and low dosage levels in the repeat mouse study be 15,000 and 7500 ppm, respectively, rather than 5000 and 1000 ppm as in the first study. The reason for this is to provide an adequate experimental basis for establishing a dose-response relationship if, in fact, a positive oncogenic response came to occur in the repeat study.

In addition, TB recommends that only male mice be tested in the repeat study because the tumors of particular concern, renal tubule adenomas, were only observed in male mice in the first study. However, since renal tubule adenomas are so rare (or at least infrequently observed), TB also recommends that larger numbers of animals be used for each dosage level to increase the statistical power of the bioassay. Possibly, 200 male mice per group may be needed.

TB, then, considers the repeat mouse study to be a specially designed study for the specific purpose of clarifying certain unresolved questions relating to the potential oncogenicity of glyphosate. Hence, the recommendations are that the study be performed at dosage levels of 30,000, 15,000, and 7500 ppm; that only male mice need be tested; and that 200 mice per group may be needed. Similarly, because of the limited nature of the concerns prompting this repeat study, TB will accept a "tier approach" to the pathological examinations in this study. First, a very thorough and complete gross necropsy should be performed on all animals in this study, particularly noting all findings suggestive of possible tumors. Second, a full and complete set of tissues/organs should be excised and fixed from each animal in the study (for possible future need). Third, it will only be necessary in the "first tier" to do the following:

1. Process and examine multiple sections of kidney and liver from all high dosage levels and control animals in the study.

2. Process and examine all grossly observed "findings" suggestive of possible tumors from all animals in all groups in the study.

If the "first tier" examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should be requested to submit a proposed protocol for the repeat mouse study to the Agency for comment before the experimental work is initiated.

Regarding the comments of Monsanto's experts (Drs. Squire, Goodman, and Stemmer), the SAP considered their opinions but nevertheless believed the mouse kidney tumors to be "equivocal" and recommended further studies in rats and/or mice. TB concurs with the viewpoint expressed by the SAP.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL
SAFETY AND POLLUTION PREVENTION

September 21, 2022

MEMORANDUM

SUBJECT: Withdrawal of the *Glyphosate Interim Registration Review Decision*

TO: Glyphosate Registration Review Docket (EPA-HQ-OPP-2009-0361)

FROM: Cathryn Britton, Branch Chief
Risk Management and Implementation Branch V
Pesticide Re-evaluation Division

THRU: Mary Elissa Reaves, Director
Pesticide Re-evaluation Division
Office of Pesticide Programs

On June 17, 2022, the United States Court of Appeals for the Ninth Circuit vacated and remanded the human health portion of EPA's interim registration review decision for glyphosate (ID), held that EPA's failure to make an effects determination before issuing the ID violated the Endangered Species Act (ESA), and remanded without vacating the ecological portion of the ID but imposed an October 1, 2022 deadline for EPA to complete the remand. *Natural Resources Defense Council et al. v. EPA*, 38 F.4th 34 (9th Cir. 2022). In light of the court's decision, this memorandum announces EPA's withdrawal of all remaining portions of the glyphosate ID, including the remanded ecological portion.

A copy of the glyphosate ID, now vacated in part and the remainder withdrawn, is posted to the glyphosate registration review public docket (EPA-HQ-OPP-2009-0361) at https://www.regulations.gov.

Background

Issuance of the Glyphosate Interim Registration Review Decision

Registration review is EPA's periodic review of pesticide registrations to ensure that each pesticide registration continues to satisfy the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration, that is, that the pesticide can perform its intended function without unreasonable adverse effects on human health or the environment. Under FIFRA section 3(g), each pesticide is required to be reviewed every 15 years.

EPA regulations establish procedures for the registration review program required in FIFRA section 3(g). Under 40 C.F.R. § 155.56, EPA may issue, when it determines it to be appropriate, an interim registration review decision before completing a registration review. Among other things, the interim registration review decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment, and completing the registration review. Procedures for issuing an interim registration review decision are set forth in § 155.58.

On February 3, 2020, EPA published a notice in the Federal Register (85 Fed. Reg. 5957) announcing the availability of the glyphosate ID. EPA issued the ID pursuant to 40 C.F.R. §§ 155.56 and 155.58, explaining that it was doing so to "(1) move forward with aspects of the registration review case that are complete and (2) implement interim risk mitigation." The ID finalized EPA's draft risk assessments supporting registration review, *Glyphosate Draft Human Health Risk Assessment for Registration Review* and *Registration Review—Preliminary Ecological Risk Assessment for Glyphosate and Its Salts*. The ID did not identify any human health risks of concern from exposure to glyphosate but did identify potential ecological risks. It also identified interim risk mitigation measures, in the form of label changes, including spray drift management language, herbicide resistance management language, a non-target organism advisory, and certain label consistency measures. It concluded that, under FIFRA, the benefits of glyphosate outweigh the potential ecological risks when glyphosate is used in accordance with labels.

The glyphosate ID did not make findings under section 7 of the ESA or under the Endocrine Disruptor Screening Program (EDSP) pursuant to section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA), nor did it respond to a 2018 administrative petition submitted by the Environmental Working Group and others (EWG et al.) to reduce the tolerance level for glyphosate residues on oats and require certain label changes based on concerns regarding dietary exposure and carcinogenicity. EPA explained that it would do so before completing registration review for glyphosate, and that the "final registration review decision for glyphosate will be dependent upon the result of the agency's ESA assessment and any needed section 7 consultation with the [U.S. Fish and Wildlife Service and the National Marine Fisheries Service], an EDSP FFDCA section 408(p) determination, and after a resolution of the EWG et al. petition." The glyphosate ID also did not solicit label changes from registrants to implement the interim risk mitigation measures. EPA explained that it would do so once it responded to the EWG et al. petition.

For further background on glyphosate and its registration review history, see the end of this memorandum.

Endangered Species Act Assessment for Glyphosate

ESA section 7(a)(2) requires that federal agencies ensure that the actions they authorize, fund, or carry out are not likely to jeopardize the continued existence of species listed as

threatened or endangered under the ESA (listed species) or destroy or adversely modify their designated critical habitat. For pesticides in registration review, EPA's responsibility includes evaluating potential effects to listed species and their designated critical habitat, often through a biological evaluation (BE). If EPA determines that a pesticide's registration "may affect" and is "likely to adversely affect" listed species or designated critical habitat, the Agency initiates formal consultation with the U.S. Fish and Wildlife Service (FWS) and/or the National Marine Fisheries Service (NMFS) (together, the Services). The Services prepare their respective biological opinions (BiOps) regarding whether the pesticide's registration is likely to jeopardize the continued existence of listed species or result in the destruction or adverse modification of designated critical habitats and describing any reasonable and prudent measures or reasonable and prudent alternatives. EPA then uses its authorities under FIFRA to implement, as necessary, any such measures or alternatives described in the BiOps.

On November 25, 2020, EPA released the draft BE for glyphosate for public comment. On November 12, 2021, EPA released the final BE for glyphosate, which found that glyphosate may affect 1,795 listed species and 792 critical habitats and is likely to adversely affect 1,676 of those species and 759 of those habitats. EPA initiated formal consultation with the Services in November 2021. As noted in the declaration filed in support of EPA's August 1, 2022 petition for panel rehearing of the Ninth Circuit's decision, discussed below, consultation with the Services is ongoing.

For further information on EPA's ESA assessment for glyphosate, see https://www.epa.gov/endangered-species/final-national-level-listed-species-biological-evaluation-glyphosate.

Challenges to Glyphosate Interim Registration Review Decision

On March 20, 2020, two groups of petitioners filed petitions for review of the glyphosate ID in the Ninth Circuit. *See Natural Resources Defense Council et al. v. EPA*, No. 20-70787 and *Rural Coalition et al. v. EPA*, No. 20-70801. Together these petitions challenged EPA's analysis of the human health and ecological risks and costs of glyphosate, weighing of such risks against the benefits of glyphosate, and the interim risk mitigation measures identified in the ID, and alleged that EPA violated the ESA by issuing the ID before completing consultation with the Services.

While EPA defended its analysis of human health risks and the alleged ESA violation, it moved for partial voluntary remand without vacatur of its analysis of ecological risks and costs, weighing of such risks against benefits, and interim risk mitigation measures. EPA sought remand to:

- Consider how the glyphosate ID may be impacted by the (then) draft BE and whether additional or different risk mitigation measures may be necessary.
- Reconsider its analysis of ecological risks as it relates to in-field effects of glyphosate on monarch butterfly habitat in light of the court decision in *National Family Farm Coalition v. EPA*, 966 F.3d 893 (9th Cir. 2020).

- Consider whether the court decision in *National Family Farm Coalition v. EPA*, 960 F.3d 1120 (9th Cir. 2020) regarding EPA's analysis of spray drift risks and other potential costs of another pesticide (dicamba) affected EPA's analysis of glyphosate.
- Evaluate the glyphosate ID in light of the change in Administration and policy priorities, as reflected in the January 20, 2021 "Executive Order on Protecting Public Health and the Environment and Restoring Science to Tackle the Climate Crisis" (86 FR 7037, 1/25/21) and, in particular, consider whether there are other aspects of its analysis of ecological risks and costs related to glyphosate that should be reassessed or for which additional explanation should be provided.
- Consider what risk mitigation measures may be necessary to reduce potential risks following completion of analyses left outstanding in the ID.

The Ninth Circuit heard oral argument on these challenges on January 10, 2022 and issued its decision on June 17, 2022. The court vacated and remanded the human health portion of the glyphosate ID, held that EPA's failure to make an effects determination before issuing the ID violated the ESA, and granted EPA's motion for partial voluntary remand but imposed an October 1, 2022 deadline for EPA "to issue a new ecological portion." *Natural Resources Defense Council et al. v. EPA*, 38 F.4th 34 (9th Cir. 2022).

On August 1, 2022, EPA filed a petition for panel rehearing that sought relief only from the court's imposition of a deadline to complete remand of the ecological portion of the ID. EPA explained that, while the court did not define what it meant by "issue a new ecological portion," the Agency would not be able to finalize a new ecological portion in a registration review decision for glyphosate by the October 1, 2022 deadline because of the time needed to address the issues for which EPA sought remand and to complete consultation under the ESA. In a declaration filed in support of the petition, EPA set forth its anticipated schedule for completing registration review for glyphosate. EPA also stated that if the court did not lift the deadline, the Agency might exercise its discretion to withdraw the remanded ecological portion of the ID and focus its efforts on the required final registration review decision for glyphosate. A copy of EPA's August 1, 2022 petition for panel rehearing and declaration filed in support of the petition is posted to the glyphosate registration review public docket (EPA-HQ-OPP-2009-0361) at https://www.regulations.gov.

On August 5, 2022, the court denied EPA's petition for panel rehearing without opinion.

Withdrawal

In its June 17, 2022 decision, the Ninth Circuit vacated and remanded the human health portion of the glyphosate ID. EPA is now withdrawing all remaining portions of the ID, including the remanded ecological portion consisting of the Agency's analysis of the ecological risks and costs of glyphosate, the weighing of such risks against the benefits of glyphosate, and interim risk mitigation measures. Because the ID is an informal adjudication that EPA issued at its discretion, EPA may withdraw all or a portion of it without public comment. Moreover, it would be impracticable for EPA to take public

comment here because of the October 1, 2022 deadline imposed by the court to complete remand of the ecological portion of the ID.

EPA has determined that withdrawal is appropriate in light of the Ninth Circuit's June 17, 2022 decision and the particular circumstances of glyphosate's registration review and ESA assessment. Insofar as the court has ordered EPA to finalize a "new ecological portion," doing so through another interim registration review decision or a final registration review decision would involve significant and lengthy steps. As detailed in EPA's August 1, 2022 petition for panel rehearing and declaration filed in support of the petition, the Agency is unable to finalize a new ecological portion in a registration review decision for glyphosate by the court-imposed October 1, 2022 deadline because of the time needed to address the issues for which EPA sought remand and to complete consultation under ESA. Moreover, before issuing such a decision, EPA must first prepare a proposed decision, make it available for a period of public comment of at least 60 days, and consider any comments received. 40 C.F.R. § 155.58. For reference, EPA received approximately 283,300 public comments comprising over 12,000 unique submissions when it published the glyphosate proposed ID in May 2019, and it then took nine months to finalize and publish the ID in February 2020. EPA cannot complete these processes by the court-imposed October 1, 2022 deadline.

To date, EPA has not solicited label changes from registrants to implement the interim risk mitigation measures identified in the ID. The Agency has not solicited such label changes because EPA's continued work towards completing registration review for glyphosate could affect what risk mitigation measures EPA may determine are necessary, as noted in the declaration filed in support of EPA's August 1, 2022 petition for panel rehearing of the Ninth Circuit's decision. Moreover, the Agency continues to work on a response to the EWG et al. petition, which asks EPA to reduce the tolerance level for glyphosate residues on oats and require certain label changes based on concerns regarding dietary exposure and carcinogenicity. Because of the court's vacatur and remand of the human health portion of the ID, EPA believes it would be appropriate to respond to the EWG et al. petition once it completes its review on remand. To avoid multiple, and potentially conflicting, rounds of label changes, EPA expects to defer solicitation of label changes until it issues a final registration review decision for glyphosate.

For these reasons, EPA believes it is appropriate to withdraw all remaining portions of the glyphosate ID, including the remanded ecological portion, and focus its efforts on completing the required final registration review decision for glyphosate.

Although the glyphosate ID is now vacated in part and the remainder withdrawn, that does not automatically mean that EPA's underlying scientific findings regarding glyphosate, including its finding that glyphosate is not likely to be carcinogenic to humans, are either incorrect or cannot be used as support for a future decision following reconsideration in accordance with the court's decision.

Next Steps

With respect to the vacated human health portion of the ID, in accordance with the Ninth Circuit's June 17, 2022 decision, EPA intends to revisit and better explain its evaluation of the carcinogenic potential of glyphosate and to consider whether to do so for other aspects of its human health analysis. With respect to the withdrawn ecological portion of the ID, EPA intends to address the issues for which it sought remand, including:

- Consider whether additional or different risk mitigation measures may be necessary based on the outcome of ESA consultation for glyphosate.
- Prepare an analysis of in-field effects of glyphosate on monarch butterfly habitat.
- Consider whether EPA's analysis of spray drift risks and other potential costs of dicamba are relevant to EPA's analysis of glyphosate's risk from spray drift.
- Consider whether there are other aspects of EPA's analysis of ecological risks and costs related to glyphosate that should be reassessed or for which additional explanation should be provided.
- Consider what risk mitigation measures may be necessary to reduce potential risks following completion of analyses left outstanding in the ID.

EPA also intends to complete ESA consultation with the Services, respond to the EWG et al. petition, and make an FFDCA section 408(p) EDSP determination before issuing a final registration review decision for glyphosate. As noted in the declaration filed in support of EPA's August 1, 2022 petition for panel rehearing of the Ninth Circuit's decision, EPA anticipates issuing a final registration review decision for glyphosate in 2026.

Glyphosate Background and Registration Review History

Glyphosate is a non-selective, systemic herbicide with products registered for use in a wide array of both agricultural and non-agricultural settings. Agricultural uses include stone and pome fruits, citrus fruits, berries, nuts, vegetables, cereal grains, and other field crops. Non-agricultural uses include residential spot treatments, aquatic areas, forests, rights-of-way, recreational turf, ornamentals, non-food tree crops, and Conservation Reserve Program land. Glyphosate products are also registered for use on the glyphosate-resistant crops, including alfalfa, corn, soybean, cotton, canola, and sugar beets.

EPA formally initiated registration review for glyphosate in 2009 with the opening of the registration review docket for the case. The following summary highlights significant milestones that have occurred during the registration review of glyphosate

- July 2009 - The *Glyphosate Preliminary Work Plan (PWP)*, the *Glyphosate Human-Health Assessment Scoping Document in Support of Registration Review*, and the *Registration Review–Preliminary Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments for Glyphosate and Its Salts* were posted to the docket for a 60-day public comment period.

- December 2009 - The *Glyphosate Final Work Plan (FWP)* was issued. Comments received on the PWP covered the following topics: opposition to the use of glyphosate, the toxicity of glyphosate formulations and inert ingredients, use and usage trends, human health risks, ecological risks, endocrine disruption, and the benefits of glyphosate. The public comments received did not change the schedule, risk assessment needs, or anticipated data requirements in the FWP.

- September 2010 - A Generic Data Call-In (GDCI) for glyphosate was issued for data needed to conduct the registration review risk assessments. All required data were submitted and reviewed. The registration review GDCI for glyphosate is considered satisfied.

- September 2015 – The Agency completed its evaluation of Tier 1 endocrine data submitted under the EDSP and published the *Glyphosate: Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen, or Thyroid Pathways*. EPA found no convincing evidence of potential interaction with the estrogen, androgen, or thyroid pathways and glyphosate was not recommended for further EDSP testing.

- December 2016 – The agency convened a FIFRA Scientific Advisory Panel meeting to consider and review a set of scientific issues related to the EPA's evaluation of the carcinogenic potential of glyphosate. The meeting agenda, the agency's cancer issue paper, charge questions for the panel, transcript, and final report are available on EPA's website: https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel. Additional supporting materials and comments received from the public can be found in docket EPA-HQ-OPP-2016-0385 at www.regulations.gov.

- December 2017 – The agency published the *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* (dated December 12, 2017), the *Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate* (dated December 12, 2017), the *Glyphosate Draft Human Health Risk Assessment for Registration Review* (dated December 12, 2017), and the *Registration Review – Preliminary Ecological Risk Assessment for Glyphosate and its Salts* (dated September 8, 2015) on EPA's website: https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate.

- February 2018 - The agency announced the availability of the human health and ecological risk assessments for a 60-day public comment period. Over 238,000 comments were received during the comment period, most of which came from various mass mail campaigns. Approximately 2,244 unique submissions were received from various stakeholders, including pesticide registrants, industry groups, farmers, grower groups, private citizens, non-governmental organizations, states, and the U.S. Department of Agriculture. The comments did not change the risk assessments or registration review timeline for glyphosate.

- September 2018 – The Environmental Working Group, joined by Ben & Jerry's Homemade, Inc., Happy Family Organics, MegaFood, MOM's Organic Market, National Co+op Grocers, Nature's Path Foods Inc., One Degree Organic Foods USA, Inc., and Stonyfield Farm, Inc. submitted an administrative petition to the Agency. The petition requested that EPA lower the tolerance for residues of glyphosate on oats and require label changes to prohibit the preharvest use of glyphosate on oats. On May 6, 2019, the Agency published a Notice of Filing of the petition in the Federal Register for a 30-day public comment period in docket EPA-HQ-OPP-2019-0066. 103,447 comments were received on the petition, most of which came from mass mail campaigns and 419 of which represented unique comments. The Agency continues to work on its response to the petition.

- May 2019 - The Agency announced the availability of the *Glyphosate Proposed Interim Registration Review Decision* (PID) for a 60-day public comment period, which was later extended to 120 days. Along with the PID, the following documents were posted to the docket:

    - *Glyphosate: Response to Comments, Usage, and Benefits* (dated April 18, 2018)
    - *Glyphosate: Response to Comments on the Human Health Draft Risk Assessment* (dated April 23, 2019)
    - *Response to Public Comments on the Preliminary Ecological Risk Assessment for Glyphosate* (dated November 21, 2018)

    During the 120-day comment period on the PID, the agency received roughly 283,300 comments. Over 12,000 unique submissions were received from various stakeholders, including glyphosate registrants, grower groups, non-governmental organizations, pesticide industry groups, states, the U.S. Department of Agriculture and members of the general public. Most comments came from mass mailer campaigns, and approximately 120 unique substantive comments were received from various stakeholders. Public comments did not change the Agency's risk conclusions but resulted in changes to the spray drift management labeling and rotational crop instructions.

- February 2020 – The Agency announced the availability of the ID. Along with the ID, the following documents were published in the docket:
    - *Response from the Pesticide Reevaluation Division to Comments on the Glyphosate Proposed Interim Decision* (dated January 16, 2020)
    - *Glyphosate Response to Comments on the Proposed Interim Decision Regarding the Human Health Risk Assessment* (dated January 13, 2019)
    - *Glyphosate: Epidemiological Review of Zhang et al. (2019) and Leon et al. (2019) publications for Response to Comments on the Proposed Interim Decision* (dated January 6, 2020)

- November 2020 - The Agency released the draft BE for glyphosate for public comment. Approximately 870 comments that pertained to the draft BE for

glyphosate were submitted, including 11 requests for extensions of the public comment period. Additionally, six mass mail campaigns were submitted with approximately 110,000 signatures.

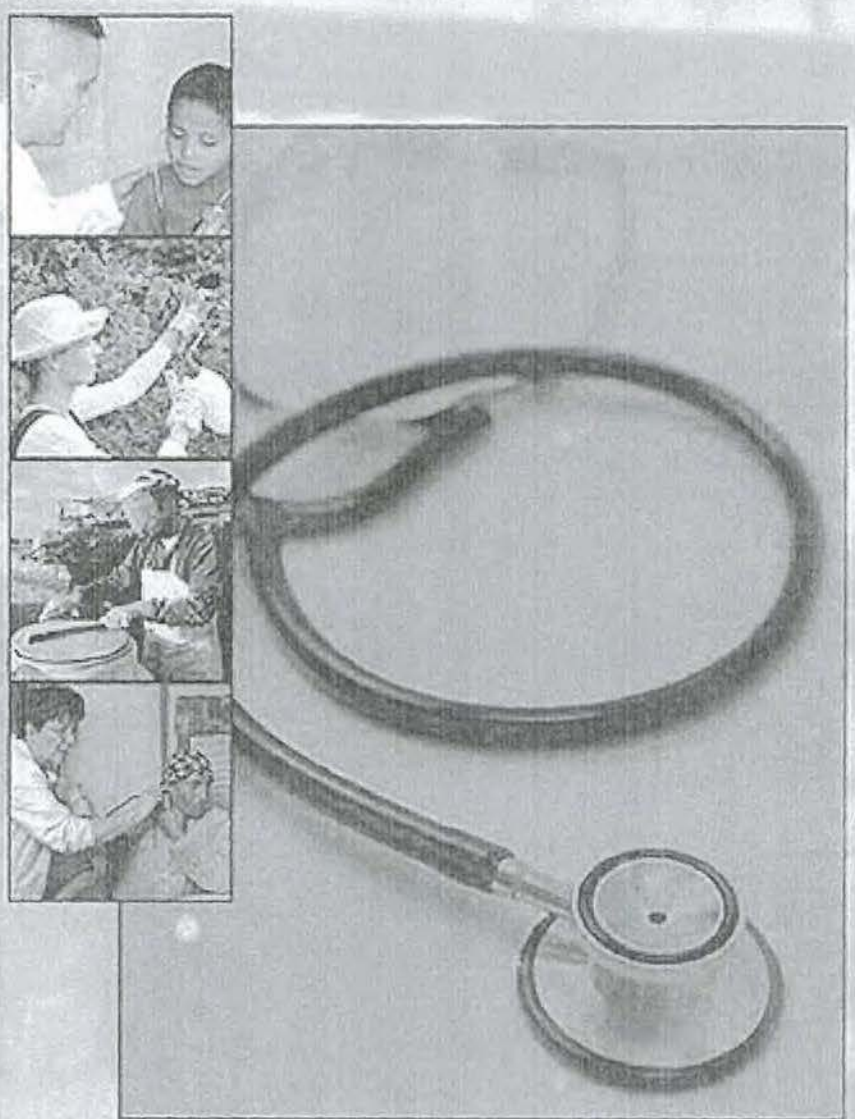
- November 2021 - The Agency released the final BE for glyphosate evaluating potential effects to listed species and critical habitats.

United States Environmental
Protection Agency
Office of Pesticide Programs

EPA 735K13001

EPA

Recognition and Management of Pesticide Poisonings



Sixth Edition

RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

Sixth Edition • 2013

James R. Roberts, M.D., M.P.H.
Professor of Pediatrics, Medical University of South Carolina

J. Routt Reigart, M.D.
Professor Emeritus, Medical University of South Carolina

Support for this publication was provided by:
Office of Pesticide Programs
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW (7506P)
Washington, DC 20460

To access the electronic version of this manual please visit:
http://www2.epa.gov/pesticide-worker-safety

This manual was developed under Cooperative Agreement No. X8-83384201, awarded by the U.S. Environmental Protection Agency (EPA) to the Medical University of South Carolina. The design and printing of this manual was facilitated by the National Association of State Departments of Agriculture Research Foundation (NASDARF) under the NASDARF Cooperative Agreement with EPA, No. X8-83456201. The information in this publication does not in any way replace or supersede the restrictions, precautions, directions or other information on the pesticide label or any other regulatory requirements, nor does it necessarily reflect the position of the EPA.

Acknowledgments

We would like to thank the Environmental Protection Agency's Office of Pesticide Programs for providing the opportunity to collaborate on this sixth edition of *Recognition and Management of Pesticide Poisonings*. We are particularly grateful to Kevin Keaney, Chief of the Pesticide Worker Safety Program, who provided the vision and support for the continuation of this manual. Elizabeth Evans, M.P.H., Environmental Protection Specialist in the Pesticide Worker Safety Program, was our project officer and provided constant oversight and assistance. We thank Khin Swe Oo, M.D., D.A.B.T., from the Toxicology and Epidemiology Branch of OPP's Health Effects Division for serving as the lead EPA final technical reviewer for all chapters. Dian D. Overbey, Environmental Protection Specialist in the Communication Services Branch, provided copy editing.

Amy K. Liebman, M.P.A., M.A., Director of Environmental and Occupational Health, Migrant Clinicians Network; Geoffrey M. Calvert, M.D., M.P.H., Senior Medical Officer with the National Institute for Occupational Safety & Health's Division of Surveillance, Hazard Evaluations, and Field Studies; and Elizabeth Evans from EPA served as co-authors on Chapter 1, *Introduction* and Chapter 2, *Making the Diagnosis.*

This edition was peer reviewed by experts in clinical toxicology. We greatly appreciate the efforts of the following reviewers:

Alvin C. Bronstein M.D., F.A.C.E.P.
Medical and Managing Director
Rocky Mountain Poison and Drug Center
Denver Health and Hospital Authority
Associate Professor
Department of Emergency Medicine
University of Colorado School of Medicine
Denver, Colorado

Catherine J. Karr, M.D., Ph.D.
Associate Professor
Departments of Pediatrics and Environmental & Occupational Health Sciences
University of Washington
Director, NW Pediatric Environmental Health Specialty Unit
Seattle, Washington

Caroline Cox, M.S.
Research Director
Center for Environmental Health
Oakland, California

Matthew C. Keifer, M.D., M.P.H.
Director, National Farm Medicine Center
Marshfield Clinic Research Foundation
Marshfield, Wisconsin

Tammi H. Schaeffer, D.O., F.A.C.M.T.
Medical Toxicologist
Rocky Mountain Poison and Drug Center
Denver Health and Hospital Authority
Assistant Professor
Department of Emergency Medicine
University of Colorado School of Medicine
Denver, Colorado

We are extremely grateful for the assistance of Katie Chamberlain, R.N., in developing this new edition. Ms. Chamberlain was instrumental in cataloguing electronic versions of all of the references from the previous edition, securing and organizing the new references, communicating with reviewers and providing editorial review. It is an understatement to say that she made this process easier than anticipated.

Sally D. O'Neal was responsible for additional editing, graphic design and formatting of this manual. Carol Black and the National Association of State Departments of Agriculture Research Foundation (NASDARF) provided financial support for the design and printing of this manual.

Bottom color photo on the cover (clinician and worker) © earldotter.com, courtesy Migrant Clinicians Network.

Table of Contents

CANCER

Epidemiological data support associations for both adult and childhood cancer,[2,3,52,53] with occupational exposure playing a role in cancer development for both adults and children. However, the most common types of cancer vary for children and adults, and as such, associations between pesticides and cancer are treated separately in this section. As noted at the beginning of this chapter, one common problem in evaluating cancer and pesticide relationships, particularly in children, is the relative rarity of cancer diagnoses.[3,53]

Several meta-analyses and systematic reviews have been published on the association between pesticide exposure and cancer. In most instances, these analyses and reviews serve as the primary source of information for the sections below on childhood and adult cancers.

Classification Systems for Carcinogenicity in Humans

All active ingredients in pesticides are required to be tested in animals or using *in vitro* tests for their likelihood of causing cancer. The Health Effects Division of the EPA's Pesticide Program performs an independent review of all the available evidence to classify active ingredients according to their potential to cause cancer. The classification systems have changed in the past 30 years from using a letter grade system originally issued in 1986 to a method that uses descriptive phrases based on the weight of evidence. Under the older letter grade system, a grade of "B" was a "probable carcinogen," "C" was equivalent to being classified as "possibly carcinogenic," "D" was "Not classifiable as to human carcinogenicity" and "E" was classified as having "Evidence for non-carcinogenicity for humans."

The current system was proposed in 1996, revised in 1999, and released as a final report, *Guidelines for Carcinogen Risk Assessment* in 2005 by the EPA. The report uses one of five specific phrases to designate carcinogenicity: "carcinogenic to humans," "likely to be carcinogenic to humans," "suggestive evidence of carcino-

Data support associations between occupational pesticide exposure and cancers in both adults and children.

CARCINOGEN CLASSIFICATION SYSTEMS AT A GLANCE

1986 EPA Classification System
- Group B: Probable human carcinogen
- Group C: Possible human carcinogen
- Group D: Not classifiable as to human carcinogenicity
- Group E: Evidence of non-carcinogenicity for humans

2005 EPA Classification System
- Carcinogenic: Carcinogenic to humans
- Likely: Likely to be carcinogenic to humans
- Suggestive: Suggestive evidence of carcinogenic potential
- Inadequate: Inadequate information to assess carcinogenic potential
- Not Likely: Not likely to be carcinogenic to humans

IARC Classification System
- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group 3: Not classifiable as to its carcinogenicity to humans
- Group 4: Probably not carcinogenic to humans

genic potential," "inadequate information to assess carcinogenic potential," and "not likely to be carcinogenic to humans." This information is available only via an emailed report from the EPA website *http://www.epa.gov/pesticides/carlist*. Although the new guidelines have been in place since 2005, not all pesticides have been evaluated under the 2005 cancer guidelines. Active ingredients in pesticides classified using the older letter designation could be reevaluated on a case-by-case basis.

Another classification system for potentially carcinogenic chemicals was established by the International Agency for Research on Cancer (IARC). This system classifies chemicals using a 1-4 grading system. A classification of 1 indicates the chemical is carcinogenic to humans. A category of 2 is split between 2A (probably carcinogenic to humans) and 2B (possibly carcinogenic to humans). A category of 3 indicates the chemical is not classifiable as to its carcinogenic potential. Generally, this category is used when there is inadequate evidence in humans or animals to establish a cancer-causing relationship. Group 4 indicates that the chemical is probably not carcinogenic to humans.

The table at the end of this chapter lists selected pesticides and their classification of carcinogenicity.

The table at the end of this chapter lists selected pesticides and their classification of carcinogenicity. The list is not meant to be all inclusive, but an attempt to list agents that are more commonly used or have a higher likelihood of being carcinogenic in humans. It includes a number of chemicals that were classified under both the newer and older EPA systems. The list includes some pyrethroid insecticides, the residential use of which has increased as many of the organophosphates have been phased out.

Associations between Childhood Cancer and Pesticides

Relationships between childhood cancers and pesticides were summarized in two review articles, the first by Zahm and Ward in 1998, and an update published in 2007 by Infante-Rivard. The pediatric cancer types with the most compelling evidence for an association with pesticides are leukemia and brain tumors. Of note, in most of the studies reviewed, all forms of leukemia were considered in one group because of insufficient numbers of certain types of leukemia – *e.g.*, acute lymphocytic leukemia (ALL) or acute myelocytic leukemia (AML). There were a few studies of sufficient size that were able to evaluate ALL separately. Brain tumors are also reported as a group rather than by individual tumor types as they are even rarer than childhood leukemia.[3,53]

The pediatric cancer types with the most compelling evidence for an association with pesticides are leukemia and brain tumors.

Childhood Leukemia

Thirteen of the 18 studies reviewed in the 1998 Zahm and Ward article found an increased risk of leukemia following pesticide exposure. The most common reported exposure was not related to agricultural production but rather household insecticide use during pregnancy or during the preconception period. As mentioned above, mixing leukemia types and recall bias were among the limitations of these earlier studies.[53]

Infante-Rivard reviewed 12 more recent studies in 2007.[3] Most of these studies were larger and used higher-quality exposure assessment methodologies. Five found statistically significant associations between leukemia and pesticide exposure.[54,55,56,57,58]

Two included a detailed exposure assessment and were able to demonstrate a dose-response effect.[56,58] The largest study included 491 subjects and limited the outcome to acute lymphocytic leukemia. In this study, maternal residential use during pregnancy of herbicides (OR = 1.84, 95% CI, 1.32, 2.57), plant insecticides (OR = 1.97, 95% CI, 1.32-2.94), and "pesticides for trees" (OR = 1.70, 95% CI, 1.12-2.59) were all associated with ALL. Childhood exposure (from birth to diagnosis of ALL) to plant insecticides (OR = 1.41, 95% CI, 1.06-1.86) and herbicides (OR = 1.82, 95% CI, 1.31-2.52) were also significantly associated.[56] Two studies by the same author did not find an association between child's residence near agriculture-related pesticide application and childhood leukemia,[59] nor maternal residence near agricultural pesticide application at the time of their child's birth and childhood leukemia.[60]

Two additional meta-analyses have been conducted that further explore associations between pesticides and leukemia and support the previously described associations. The first meta-analysis examined parental occupational exposure to pesticides and leukemia and the second focused on studies of pesticides in the home and garden.[61,62] In the first study, maternal occupational exposure was found to be associated with leukemia, the reported ORs were 2.09, 95% CI, 1.51-2.88 for overall pesticide exposure; 2.38, 95% CI, 1.56-3.62 for insecticide exposure; and 3.62, 95% CI, 1.28-10.3 for herbicide exposure. No associations were found for paternal occupational exposure.[62] In the meta-analysis focused on exposure through home and garden uses of pesticides, 15 studies were included and exposure during pregnancy to unspecified pesticides, insecticides and herbicides were all associated with leukemia (OR = 1.54, 95% CI,1.13-2.11; OR = 2.05, 95% CI, 1.80-2.32; and OR = 1.61, 95% CI, 1.2-2.16, respectively).[61]

Childhood Brain Tumors

In the 1998 Zahm and Ward review, 12 of the 16 studies presented evidence of an association between pesticide exposure and childhood brain tumors, and seven of these reached statistical significance. Similar to the findings with leukemia, household use by the parent (home and garden and on household pets) were the most commonly associated exposures. The number of children with brain tumors is even fewer than that of leukemia, so all types of brain tumors were used to define "cases."[53]

As noted with leukemia, the body of evidence estimating an association between brain tumors and pesticides since 1998 is more robust, with larger studies and improved exposure assessment. Nine of 10 studies in the 2007 Infante-Rivard review demonstrated an increased risk of brain tumors following maternal and/or paternal exposure, with three of the studies reaching statistical significance.[63,64,65] For all studies, it appeared that prenatal exposure to insecticides, particularly in the household, as well as both maternal and paternal occupational exposure before conception though birth represented the most consistent risk factors.[63,64,65,66,67,68,69,70,71] The largest case/control study (321 cases) limited the case definition to astrocytomas and noted an OR of 1.9, 95% CI, 1.1-3.3, following maternal preconceptual/prenatal exposure to insecticides.[65] One cohort study followed 235,635 children and found an association between all brain tumors and paternal exposure to pesticides immediately before conception (RR = 2.36, 95% CI, 1.27-4.39.[63]

In summary, there is relatively consistent evidence for an increased risk of developing some types of childhood cancers following preconception and/or prenatal exposure to pesticides. The strongest evidence appears to be for ALL, the most common form of childhood leukemia. Maternal exposure to insecticides and paternal occupational exposure appear to carry the greatest risk.

There is evidence for increased risk of developing some types of childhood cancers following preconception and/or prenatal exposure to pesticides.

Associations between Pesticides and Cancer in Adults

Bassil et al. conducted a systematic review of cancer and pesticides, which included studies of children and of adults. Each study was evaluated for methodological quality by two trained reviewers using a standardized assessment tool with a high inter-rater reliability. Only studies with a global rating of 4 or higher were included in the review.[2]

Many of the studies evaluating relationships between cancers in adults and pesticides are conducted in the occupational setting. Associations between pesticide exposure and the development of leukemia and non-Hodgkin lymphoma were noted in most studies. Solid tumors of the prostate, pancreas, kidney and breast were among the more consistently reported findings in studies of adults. As was noted in numerous studies of childhood outcomes, ascertainment of whether exposure actually occurred and the amount of exposure are recurring weaknesses in adult studies.

Tumors of the prostate, pancreas, kidney and breast have been among the more consistently reported findings.

Non-Hodgkin Lymphoma and Other Hematopoietic Cancers

Of the 27 studies on non-Hodgkin lymphoma (NHL) that met quality criteria in the Bassil review, 23 found positive associations. Almost half of these studies were conducted in adult cohorts of various occupational groups including farmers, pesticide applicators, landscapers and those who worked in pesticide manufacturing. Ten of the 12 cohort studies reported a positive association, with four reaching statistical significance. One of the larger cohort studies demonstrated a relative risk RR of 2.1, 95% CI, 1.1-3.9. Eleven of the 13 case-control studies (excludes one positive study in children) also demonstrated an association between occupational exposure and NHL, with 7 reaching statistical significance. Multiple classes of pesticides were implicated.[2]

A separate meta-analysis of case-control studies examining the relationship between pesticide exposure and hematopoietic cancers was published in 2007. The authors reviewed 36 case-control studies. After excluding studies with methodological flaws or data concerns, a study that included non-hematopoietic cancers and a study written in Italian, 13 studies remained for analysis. The cancers assessed in the meta-analysis were NHL, leukemia and multiple myeloma.[72] The overall meta-OR for NHL was 1.35, 95% CI, 1.2-1.5. An increased risk for leukemia and multiple myeloma was also demonstrated, though both were just short of reaching statistical significance (OR = 1.35, 95% CI, 0.9-1.2 and OR = 1.16, 95% CI, 0.99-1.36). The authors also conducted a meta-regression to account for the heterogeneity among the studies. They found that exposure for longer than 10 years increased the risk for all hematopoietic cancers (mOR = 2.18, 95% CI, 1.43-3.35) and for NHL (mOR = 1.65, 95% CI, 1.08-2.51).[72]

As with other cancer epidemiologic studies discussed above, the major limitation was the lack of sufficient exposure information in many of the studies. Additionally, the cohort studies in the above meta-analysis only listed the class of pesticide and the corresponding OR (herbicides or insecticides) rather than the individual pesticide.[72] Other individual studies have demonstrated risks from certain specific pesticides. One well-designed cohort study reported risks associated with mecoprop, a chlorophenoxy herbicide.[73] Another study demonstrated risks from another chlorophenoxy herbicide – methyl phenoxyacetic acid (MCPA) – and from glyphosate.[74] Another study demonstrated a significant increased risk of NHL for subjects exposed to 2,4-D.[75] The Agricultural Health Study demonstrated a risk of developing leukemia following exposure to diazinon.[76]

Prostate Cancer

It has been suspected that pesticide exposure may be associated with prostate cancer. This association may be related to hormonally active pesticides, known as endocrine

disruptors.[77] Of the eight studies included in the Bassil review, all showed positive associations between pesticide exposure and prostate cancer.[77,78,79,80,81,82,83,84] A particularly well-designed study from the Agriculture Health Cohort included 55,000 men in Iowa and North Carolina. The authors found that farmers who applied pesticides had a small but significant increase in prostate cancer compared to the general male population in Iowa and North Carolina (standardized prostate cancer incidence ratio of 1.14 (1.05-1.24)). The study also evaluated risk to specific pesticides by inquiring about 50 different pesticides to which the farmer was "ever exposed" and found positive associations with carbofuran, permethrin, aldrin and DDT. Each OR was in the range of 1.25 to 1.38, all with statistically significant 95% CIs. However, among those who were in the "highest exposure category," a risk estimate of 3.47, 95% CI, 1.37-8.76, was noted for the fumigant methyl bromide. In addition, six pesticides (chlorpyrifos, fonofos, coumaphos, phorate, permethrin and butylate) were positively associated with prostate cancer in men with a family history of prostate cancer.[83]

Around the same time as Bassil's review was published, Mink et al. conducted a separate review article on prostate cancer. The two authors reviewed and independently assessed each study for inclusion or exclusion, and discrepancies were reconciled. The authors included 13 studies (8 cohort, 5 case-control) in their final review; however, they did not report the total number of studies reviewed and excluded. Despite some scattered positive findings in some of the studies they reviewed, the authors concluded there was no causal link between pesticides and prostate cancer.[52]

Two case-control studies by Settimi et al. evaluated prostate cancer among agricultural workers and included a comprehensive questionnaire to evaluate exposures as well as potential confounders. The first study evaluated numerous types of cancers and demonstrated an excess risk of prostate cancer among farmers and farmworkers (OR = 1.4, 95% CI, 1.0-2.1). When the analysis was limited to those who applied pesticides, the OR = 1.7, 95% CI, 1.2-2.6.[85] Assessment of pesticide classes and individual pesticides within classes demonstrated risk specificity for organochlorine insecticides. Elevated ORs for prostate cancer were found for "ever being exposed" to all organochlorines, DDT and dicofol and tetradifon. All ORs were statistically significant, and were slightly higher for those who reported greater than 15 years of exposure compared to "ever exposed."[78]

Another case-control study included data on exposure, diet, lifestyle and occupational factors. A positive association was found for exposure to pesticides, but the 95% CIs were wide. This may have been attributable to the small size of the study – 40 cases – and fewer reporting exposure to pesticides.[86] Two other case-control studies found no association with prostate cancer and pesticide use.[87,88]

Tumors of the Kidney

A recent review article evaluated renal cancer in adults (primarily renal cell carcinoma) following occupational exposure to pesticides. This review included four studies, each of which observed positive associations between pesticides and renal cancer.[89,90,91,92]

Other Associations between Human Cancer and Pesticides

Several different agents used as wood preservatives are currently classified as probable carcinogens. Pentachlorophenol (PCP) has been classified as a B2 (probable human carcinogen). In humans, it has been associated with soft tissue sarcoma and kidney and GI tract cancers; however, a causal link has not been established.[89,93] In animal data submitted to the U.S. EPA in support of re-registration of PCP liver tumors, pheochromocytomas and hemangiosarcomas were noted, supporting the B2 classification.[94]

Arsenic is well established as a human carcinogen. Studies show that arsenic exposure can result in epigenetic dysregulation including DNA methylation, histone

modification and microRNA expression. These alterations may play a mechanistic role in cancer development, but long-term studies have not yet confirmed this.[95] Primary cancers caused by arsenic include tumors of the lung, bladder and skin. On occasion, the hyperkeratotic papules described above have undergone malignant transformation. Years after exposure, dermatologic findings include squamous cell and basal cell carcinoma, often in sun-protected areas.[96]

A recent review of lung cancer and arsenic evaluated nine cross-sectional studies, six cohort studies, and two case-control studies. Despite the limitations of some of the study designs, the risk ratios and standardized mortality ratios were consistently high on nearly all of the studies. The evidence was most consistent at high exposure levels. The evidence was weak or lacking for developing cancer from exposure to lower levels of arsenic via contaminated drinking water (<100 µg/L).[97]

ENVIRONMENTAL ENDOCRINE DISRUPTOR EFFECTS

Data relating human endocrine disruption has become progressively stronger in supporting a role of pesticides. Extensive research continues in this area of investigation.

Over the last 15 years there has been increasing interest in the ability of environmental chemicals to disrupt endocrine systems. Many pesticides, pesticide vehicles and contaminants have endocrine-disrupting properties based on *in vitro* and animal studies. While data on human effects remain somewhat fragmentary and inconclusive, the weight of evidence from multiple lines of investigation appears to support the concern for human effects. These effects are discussed briefly below, along with the literature that supports these assertions.

The cellular biology of endocrine disruption is very complex and has been extensively reviewed. While the details are beyond the scope of this manual, the reader is directed to one of several reviews for more specific information.[98,99,100] As a group, exogenous agents including pesticides that affect the endocrine system have been labeled endocrine disruptive chemicals (EDCs). Several basic mechanisms have been identified, including direct interaction with nuclear receptors (NR), disturbance of NR signaling and changes in hormone availability. *In vitro* evidence of the latter exists for several pesticides, by alteration of P450 enzyme activity that influences the availability of steroid hormones either by increasing or decreasing the rates of metabolism. For instance, methoxychlor has been shown to interfere with 5'deiodinase in the liver.[101]

Animal Toxicology

Animal studies conducted in the laboratory suggest that some pesticides may disrupt the endocrine systems of a variety of animals. Vinclozolin, a fungicide with low acute toxicity, has been shown to be strong antiandrogen in rats when exposure occurs *in utero*.[102] Exposure of female rats to DDT has been shown to lead to precocious puberty.[103] Lindane has been shown to affect adrenal steroid synthesis.[104] There is considerable evidence that a variety of chemicals, including some pesticides, affect thyroid function in animals.[105,106]

Further support for effects comes from observations in wildlife. These studies represent the most robust evidence base for various endocrine effects from many different pesticide classes. Only a few examples are mentioned because of space constraints. A strong antiandrogen effect was shown in alligators in a lake in Florida in response to heavy contamination with pesticides including dicofol, DDT and DDE.[107,108] Likewise, a relatively strong association has been shown between the biocide tributyltin (TBT) and pseudohermaphroditism in 150 species of snails.[109] Marine mammals have been noted to have high levels of contamination with a variety of chemicals including pesticides such as DDT, DDE, mirex, dieldrin and chlordane metabolites.[110] These contaminants have been potentially linked to reproductive failure and other effects due to their endocrine action. For example, PCBs in seals and polar bears have